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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/375,924	08/17/1999	MICHAEL GALLO	ABGX-2-CIP	5797

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ROPES & GRAY LLP
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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

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10/29/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/375,924	GALLO ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 6/29/04 is acknowledged and has been entered.

Claims 52-61 are pending and are being examined.

The following ground of rejection remains.

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 52-61 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/18412 (IDS reference) in view of Kim et al (Scand. J. Immunol. 40, 457-465, 1994, IDS reference), Kim (Eur. J. Immunology 1994, 24: 2429-2434, IDS reference) and WO 97/34631 (IDS reference) and known facts disclosed in the instant specification on page 41 at lines 24-30.

WO 96/18412 teaches chimeric proteins comprising IgG hinge region and a half-life increasing polypeptide such as the Fc region of an IgG molecule, the Fc region meaning that IgG terminal domain that is produced upon papain digestion of IgG, i.e., comprises a CH2 and CH3 region (especially abstract, page 9 at lines 4-14, page 10 at lines 18-23). WO 96/18412 also teaches that the entire Fc region can be used, or only a half-life enhancing portion.

WO 96/18412 does not teach wherein the said protein is an antibody with an extended serum half-life comprising a first IgG region capable of binding FcRb and at least a second IgG region capable of binding FcRb, wherein at least second IgG regions confers upon said antibody avidity of binding to FcRb receptor at pH 6.0 greater than that of said antibody lacking said at least second IgG region, said second region capable of binding in a pH dependent manner, and the other limitations recited in the instant claims, nor a method for

extending the serum half-life of an antibody by linking the first and at least second IgG regions to create the antibody of the instant product claims.

Kim et al (SJI) teach the necessity for two functional catabolic sites per Fc for serum persistence, and that the increase in avidity of Fc fragments brought about by the presence of two sites per molecule results in improved binding to protective receptor (i.e., FcRb). Kim et al further teach that tagging of a protein with an Fc-derived fragment containing only one functional catabolic site would be predicted to be ineffective in significantly extending the half-life (especially discussion section). Kim et al teach that regions within both the CH2 and the CH3 domains are involved in catabolic control.

Kim et al (EJI) teach pH dependence, i.e., binding at pH of 6-6.5 and release at pH 7.4, of IgG1 or Fc fragment binding to FcRn (i.e, FcRb) and that the presence of two FcRn binding sites per Fc hinge fragment enhance binding to FcRn. Kim et al teach FcRn site is localized to residues at the CH2-CH3 interface.

WO 97/34631 teaches antibody constant domains can be combined with another immunoglobulin domain or with any other protein, that the Ig constant domains may be expressed in combination with an Fc domain or an entire Fc-hinge domain to produce a recombinant protein with enhanced biological stability (especially paragraph spanning pages 15 and 16 and claims 4, 8, 12, 13, 14).

The known facts disclosed in the instant specification on page 41 at lines 24-30 are that IgG1 has an additional, i.e., unpaired, cysteine capable of disulfide bond formation.
It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have extended the serum half life of an antibody as taught by WO 97/34631 by making an antibody comprising the protein taught by WO 96/18412 and further comprising an Fc IgG region capable of binding FcRb in a pH dependent manner as taught by Kim et al (SJI) and Kim et al (EJI). In addition, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a mutated hinge region without the unpaired cysteine disclosed as a known fact in the instant specification.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to produce a protein with increased serum persistence and avidity of binding to FcRb as taught by WO 96/18412, Kim et al (SJI) and Kim et al (EJI), and because Kim et al (SJI) and Kim et al (EJI) teach the need for two FcRn binding sites to significantly increase half life and because WO 97/34631 teaches that Ig constant domains may be expressed with an Fc domain or an entire Fc-hinge domain to produce a recombinant protein with enhanced biological stability. One of ordinary skill in the art at the time the invention was made would have been motivated to mutate the hinge region to remove or change the unpaired cysteine in order to insure that no additional reactivity would interfere with increased serum half life or function of the antibody due to disulfide bond formation through the unpaired cysteine.

It is of record in the Office Action mailed 2/16/00 at item #10 that FcRp and FcRn are the same receptor.

Applicant's arguments in Applicant's amendment filed 6/29/04 have been fully considered, but are not persuasive.

Applicant's arguments in the said amendment are of record on pages 2-120, briefly that none of the cited references disclose the explicit claim limitation that the antibody whose half-life is to be extended is already capable of binding FcRn, that Strom (WO 96/18412) teaches away from using an antibody as the portion of a chimeric protein comprising an IgG Fc region, that Kim I teaches that tagging of a protein with an Fc-derived fragment containing one functional catabolic site would be predicted to be ineffective in extending the protein's serum half life, that along with Kim II, Kim I teaches that a two functional catabolic sites are necessary for FnRn binding, that neither teach that the serum half life of a protein such as an antibody could be extended by fusing an additional functional catabolic site to the end of each of the two fragments of a dimer, that Ward et al (WO/97/34631) teach that to extend the serum half life of an antibody or protein that is already capable of binding FcRn, the protein is mutated directly at critical residues in the already existing FcRn binding sites and so teaches away from the claimed invention, that the claims of Ward et al teach a fusion method for proteins that are not already capable of binding FcRn.

It is the Examiner's position that Strom et al does not teach away from using antibodies as the portion of a chimeric protein comprising an IgG Fc region because the teaching on page 10 of Strom at lines 11-15 is merely the definition of a cytokine as a non-antibody protein, i.e., Strom teach that "By "cytokine" is meant any of the non-antibody proteins released by one cell population (e.g., primed T lymphocytes) on contact with specific antigen, which act as intercellular mediators, as in the generation of an immune response. One important class of cytokines are those which induce proliferation of lymphocytes, e.g., T cells." One of ordinary skill in the art would have been aware that some cytokines also act to stimulate B cell proliferation and antibody production, as taught by Strom in the paragraph spanning pages 1 and 2, i.e., the conditions being treated by extending the half-life of cytokines by using a chimeric protein comprising an IgG Fc region stimulate both arms of the immune response, T cell and B cell.

It is the Examiner's position that Kim et al ("Kim I") teach that a CH_2-hinge dimer has a longer half-life than the monomer, that the WT Fc-hinge fragment is a dimer and it had comparably long half-life to IgG, and that for serum persistence the requirement for two functional catabolic sites per IgG molecule has important implications for modifying pharmocokinetics of the therapeutic proteins by tagging with IgG domains (page 461, Table 1, Discussion). It is the Examiner's position that Kim et al teach that tagging of a protein with an Fc-derived fragment containing one functional catabolic site would be predicted to be ineffective in *significantly* extending the protein's serum half life because Kim I teach that 2 catabolic sites are required for significant serum persistence. It is the Examiner's position that

one of ordinary skill in the art would be aware from the teaching of WO 96/18412 that an Fc region of an IgG molecule contains 2 catabolic sites.

It is the Examiner's further position that regardless of what embodiments are preferred in the teaching of Ward et al or what embodiments are actually exemplified, Ward et al teach on page 8 at the first paragraph that the antibody constant domains of the present invention may also be combined with another immunoglobulin domain, the immunoglobulin constant domains may be expressed in combination with one, two, three or more domains, such as for example, a CH_2 domain, and Fc domain, or an entire Fc-hinge domain, and that the Fc or Fc-hinge domains may be linked to any protein to produce a recombinant fusion with enhanced biological stability, *or* certain mutants may be employed to create antibodies or fusion proteins with increased half lives; it is the Examiner's position contrary to Applicant's assertion that reference in the alternative constitutes an implication that the fusion method was not contemplated to apply to antibodies that any protein includes the antibodies as taught on page 3 of Ward et al. It is the Examiner's position that Ward et al teach both conjugation of antibodies with a moiety that has an increased serum half-life through its interaction with FcRn that the methods include methods of increasing the FcRn binding affinity of an FcRn binding protein or peptide so that the protein or peptide will have an increased half-life, and also teach in addition mutating amino acid residues that directly interact with FcRn (page 3). Claim 11 of Ward et al is directed to a method of increasing the serum half-life of an agent comprising conjugating said agent that is an antigen binding polypeptide, i.e., and immunoglobulin, to a mutant IgG or IgG Fc hinge fragment having an increased serum half life. In contrast to Applicant's assertion, claim 13 is drawn to an agent that is an antigen binding polypeptide, not to a variable region of an antibody. There is no recitation in the said claim that the fusion method is for proteins that are not already capable of binding FcRn.

With regard to Applicant's arguments to secondary considerations on pages 9 and 10 of Applicant's said amendment, Applicant's "Exhibit I" is has not been received by USPTO and therefore has not been considered.

4. No claim is allowed.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Wednesday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
October 18, 2004

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600